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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/554,414	09/06/2000	Moshe Szyf	2055MC/48896	9016

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EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/554,414

Applicant(s)

SZYF ET AL.

Examiner

Malgorzata A. Walicka

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 March 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 32-34 and 41-44 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 32-34 and 41-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application March 15, 2005, after final rejection. Applicant's submission of Response on March 15, 2005 is acknowledged. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Amendments to the claims have been entered as requested. Claims 1-31, 37 and 38 have been previously cancelled. Claim 32 is amended by the current amendment; claims 37-40 are cancelled and new claims 41-44 are added. Claims 32-34, and 41-44 are pending and under examination.

DETAILED ACTION

1. Restriction/election

The amended claims 32-34, and new claims 41-44 are directed to the invention that is patentably distinct from then the invention elected on Feb. 19, 2003 and prosecuted thus far. On Feb. 19, 2003 Applicants elected Group XIII-2 which related to the use of an antagonist or inhibitor of the human DNA demethylase of SEQ ID NO: 2 for restoring an aberrant methylation pattern in a patient DNA, or for changing a methylation pattern in the patient DNA. With regard to the requirement for election of species, Applicants elected the following species: double stranded oligonucleotides and antisense oligonucleotides of DNA demethylase.

The current claims are directed to the method of altering a demethylation activity of DNA demethylase in a cell-free system by a double stranded C^mG oligonucleotide, an anti-DNA demethylase antibody, and an antisense oligonucleotide of DNA demethylase, imidazole and derivatives of imidazole.

In the view that this is the first Office Action on merits after filing the RCE request, the examiner permits the shift of invention. However, if claims to the originally elected invention are reintroduced following this 1st Action on the merits after the RCE, they will be withdrawn as directed to a non-elected invention held non-responsive if all claims to the currently examined invention are cancelled. Objections and rejections of the previous prosecution are moot in the light of the shift of invention.

2. Priority

Applicants' comments on priority of the polypeptide consisting of amino acids 150-411 of SEQ ID NO: 2 dating back to May 11, 1998, i.e., the time of filing of the Canadian application which matured into the Canadian Patent 2,230,991, is acknowledged. The priority for disclosing DNA demethylase consisting of amino acids 150-411 of SEQ ID NO: 2 is granted.

3. Objections

The specification is objected to for the confusing description of Fig. 2. On page 8, line 26 one reads: "DNA dMTase is a protein inhibited by RNA". A careful inspection

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of Fig. 2 indicates that dMTase is inhibited by RNase. The same error is repeated in the subtitle on page 26.

Description of Fig. 14 B is confusing. The data in figure 14 B were obtained *in vivo*. The description suggests *in vitro* results. In addition, the specific inhibitor is not identified in the description or in the figure.

Claim 32 is objected to for recitation "an antagonist or inhibitor". Both terms have the same meaning.

4. Rejections

4.1. 35 USC, section 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 32 –34 and 41- 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32–34 and 41- 44 are rejected as confusing. The claims are directed to the method of altering methylation activity of DNA demethylase. DNA demethylase (dMTase), by definition, possesses a demethylation activity. For examination purposes the examiner assumes that Applicants intended to claim a method of altering the demethylation activity.

In addition, claims 32 and 42 are confusing because the claims are directed to a method of inhibiting demethylase, in cell-free system, wherein an antisense oligonucleotide of DNA demethylase is going to be used as an inhibitor. An antisense oligonucleotide may alter demethylation action of DNA demethylase *in vivo*, in a cell, preventing or inhibiting expression of the gene encoding the enzyme, however it does not influence the activity of the enzyme itself.

In addition, claims 32 –34 are confusing as directed to the method of inhibiting DNA demethylase by double stranded oligonucleotide containing C^mG as a basic structural unit. The oligonucleotide of this structure is a substrate for the enzyme (see page 24 line 11 of the specification), so it cannot be used as an inhibitor in the claimed method. It may be used as an *in vivo* inhibitor, because, after entering the cell, it will competitively inhibit demethylase, which will act on it as a substrate instead of acting on the methylated genomic DNA, but *in vitro* it is a substrate not an inhibitor.

4.2. 35 USC section 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 42 is rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility. The claim is directed to a method of altering a

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demethylation activity of DNA demethylase in a cell-free system by an antisense oligonucleotide of DNA demethylase. Demethylase, as disclosed by Applicants and known in the art, is an enzyme that demethylates methylated cytosine present in DNA of a cell. The cytosine is methylated in result of action of a methylase. Thus, a substrate for the DNA demethylase is a DNA molecule or a polynucleotide, or oligonucleotide comprising cytosine methylated in position 5 (methyl-CpG) present mainly in CG islands of genomic DNA. An antisense oligonucleotide does not comprise methylated cytosines and for that reasons cannot be a substitute of demethylase substrate and, therefore, cannot inhibit demethylase by competitive inhibition. The antisense oligonucleotide acts as an antisense inhibitor of the expression of the demethylase gene.

4.3. 35 USC, section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4.3.1. Lack of written description

Claim 32, 42 and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably

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convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to altering a demethylation activity of DNA demethylase comprising amino acids 150-411 of SEQ ID NO: 2 by derivatives of imidazole. On Fig.16 Applicants demonstrate the inhibitory effect of imidazole on the enzyme. On page 43 line 25 Applicants write, "The graph clearly demonstrates a dose dependent inhibition of DNA dMTase activity by imidazole, and validates a rationale for testing imidazole based molecules [emphasis added] as inhibitors of DNA dMTase activity (Fig.16)." Thus, Applicants only suggest testing imidazole derivatives for their ability to inhibit the enzyme. Applicants do not teach any imidazole derivative that has the claimed property. Teaching one representative of the genus of imidazole derivatives, i.e., imidazole itself, does not provide structural identification of the entire genus. In conclusion, one skilled in the art is not convinced that Applicants were in possession of the claimed invention at the time the application was filed.

In addition, claims 32 and 42 are rejected because the specification does not teach that the antisense DNA inhibits the demethylating activity of DNA demethylase. This is a complete lack of written description, and one skilled in the art is not convinced that Applicants were in possession of the claimed invention at the time the application was filed.

4.2.2. Scope of enablement

The amended claims 32 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of demethylase activity by imidazole, does not reasonably provide enablement for inhibition of the demethylase activity by any imidazole derivative. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention.

Factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses altering demethylase activity of demethylase comprising amino acids 150-411 of SEQ ID NO: 2, by any derivatives of imidazole. The one skilled in the art realizes that there are many imidazole derivatives, however, the Applicants provide no guidance what is the specific structural feature, which is related to the inhibitory capability. While enablement is not precluded by additional experimentation, when an intensive experimentation is

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necessary Applicants should provide direction in which experimentation should proceed so that it was successful. Providing evidence that imidazole itself is an inhibitor is not sufficient to use any of its derivatives as the inhibitor, absent teaching how to change its structure so that the new compound still was an inhibitor.

In conclusion, without further guidance on the part of Applicants as to structural details of the recited inhibitors, experimentation left to those skilled in the art has a low probability of success and is improperly extensive and undue.

Claim 32 is additionally rejected for scope of enablement because the specification, while being enabling for inhibition of demethylase activity by imidazole, does not reasonably provide enablement for inhibition of the demethylase activity by an antisense oligonucleotide of DNA demethylase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claim.

The claim is directed to a method of altering a demethylation activity of DNA demethylase in a cell-free system by an antisense oligonucleotide of DNA demethylase. Demethylase, as disclosed by Applicants and known in the art, is an enzyme that demethylates methylated cytosine present in DNA of a cell. The antisense oligonucleotide acts as an antisense inhibitor of the expression of the demethylase gene. Applicants failed to teach how to use any oligonucleotide antisense for DNA demethylase for inhibiting the activity of the enzyme. Applicants thus, force the one skilled in the art to experimentation having a very low probability of success taking into account the fact that the antisense oligonucleotide does not comprise methylated

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cytosines and for that reasons cannot be a substitute of demethylase substrate and, therefore, cannot inhibit demethylase by competitive inhibition. Without a further guidance on the part of Applicants as to how to use the antisense oligonucleotide to inhibit activity of demethylase, experimentation left to those skilled in the art has a very low probability of success and is improperly extensive and undue.

5. Conclusion

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m.

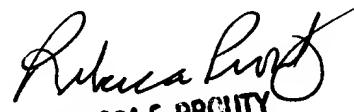
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Malgorzata A. Walicka, Ph.D.

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Patent Examiner


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